**ANTINEOPLASTIC DRUGS 1—INTRO AND BASIC PRINCIPALS**

Qs at beginning and Objectives I

1. what is …
   1. a cancer stem cell
   2. fractional kill hypothesis?
2. when adjuvent chemo used
3. what is an oncogene
4. what is a tumor suppressor
5. what is a major target of cancer therapy
6. Objectives

* **Explain the concept of “total cell kill” in cancer patients.**
* **Explain the term cell cycle specificity and be able to classify the various anticancer drugs based on the cell cycle specificity.**
* **Explain the role of oncogenes and tumor suppressor genes in cancer.**
* **Explain the mechanisms of resistance to anticancer drugs.**
* **Explain the concept of adjuvant chemotherapy**

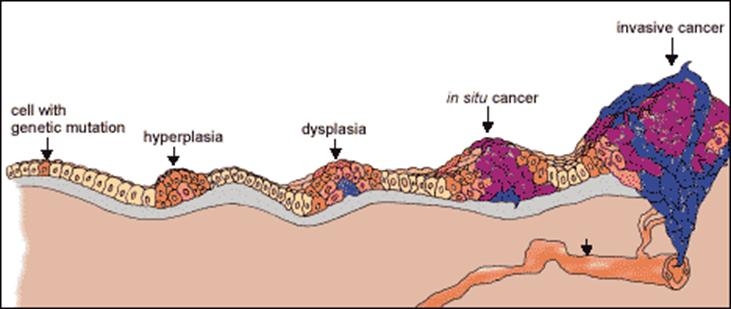
**CHEMOTHERAPY**

* Cytotoxic agents
  + generally given by intravenous injection or orally
* Most cancer drugs act by damaging DNA or inhibiting DNA synthesis
* Important exceptions are drugs that target microtubules
* Newer cancer drugs are more specific
* Some can cause cancer down the line

**THERE ARE THREE BASIC TREATMENT POSSIBILITIES FOR CANCER: SURGERY, RADIOTHERAPY, AND CHEMOTHERAPY**

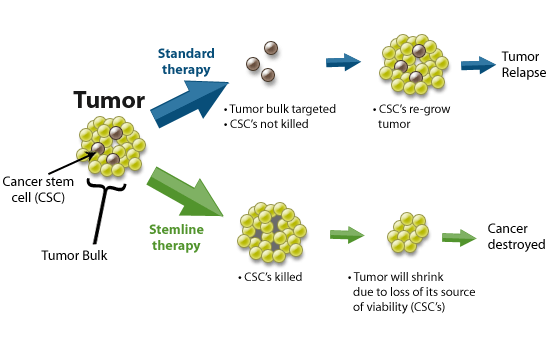
* Some cancers where chemotherapy works very well
  + Childhood leukemia
  + Retinoblastoma
  + Osteosarcoma
  + Testicular cancer
  + Hodgkin’s Disease
  + Some lymphomas
  + Some early breast cancers
* Cancers that are very difficult to treat with chemotherapeutics alone (need surgery or radiotherapy first
  + Colon
  + Lung
  + Late stage breast cancer
  + Pancreatic cancer

**CANCER DEVELOPMENT**



* proteins on the surface of a cancer cell is critical for its ability to be able to metastasize
* dysplasia is when cells start changing and you get a mixture of cell types

**CANCER STEM CELLS**

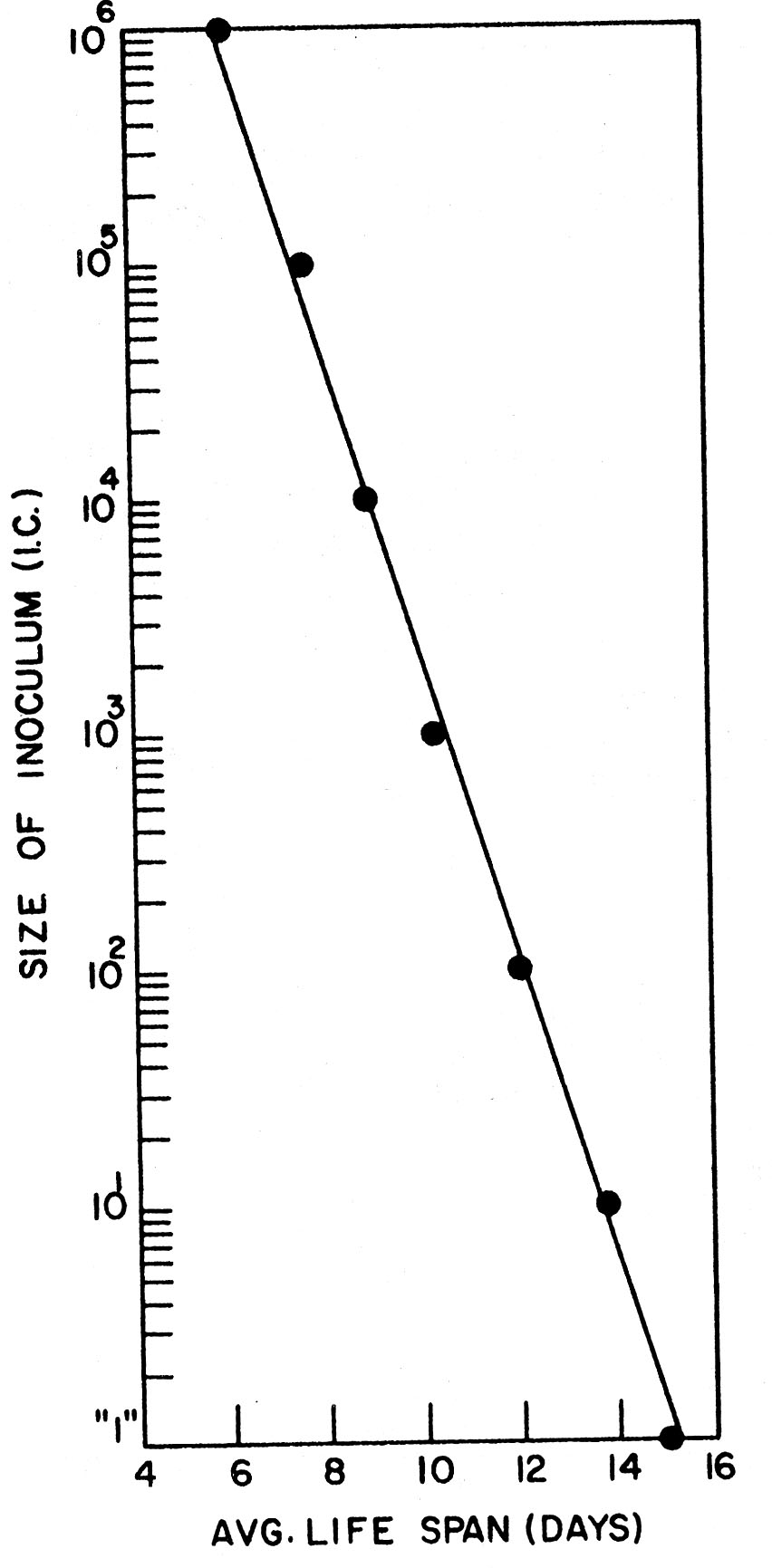
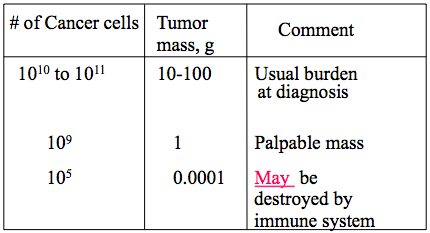
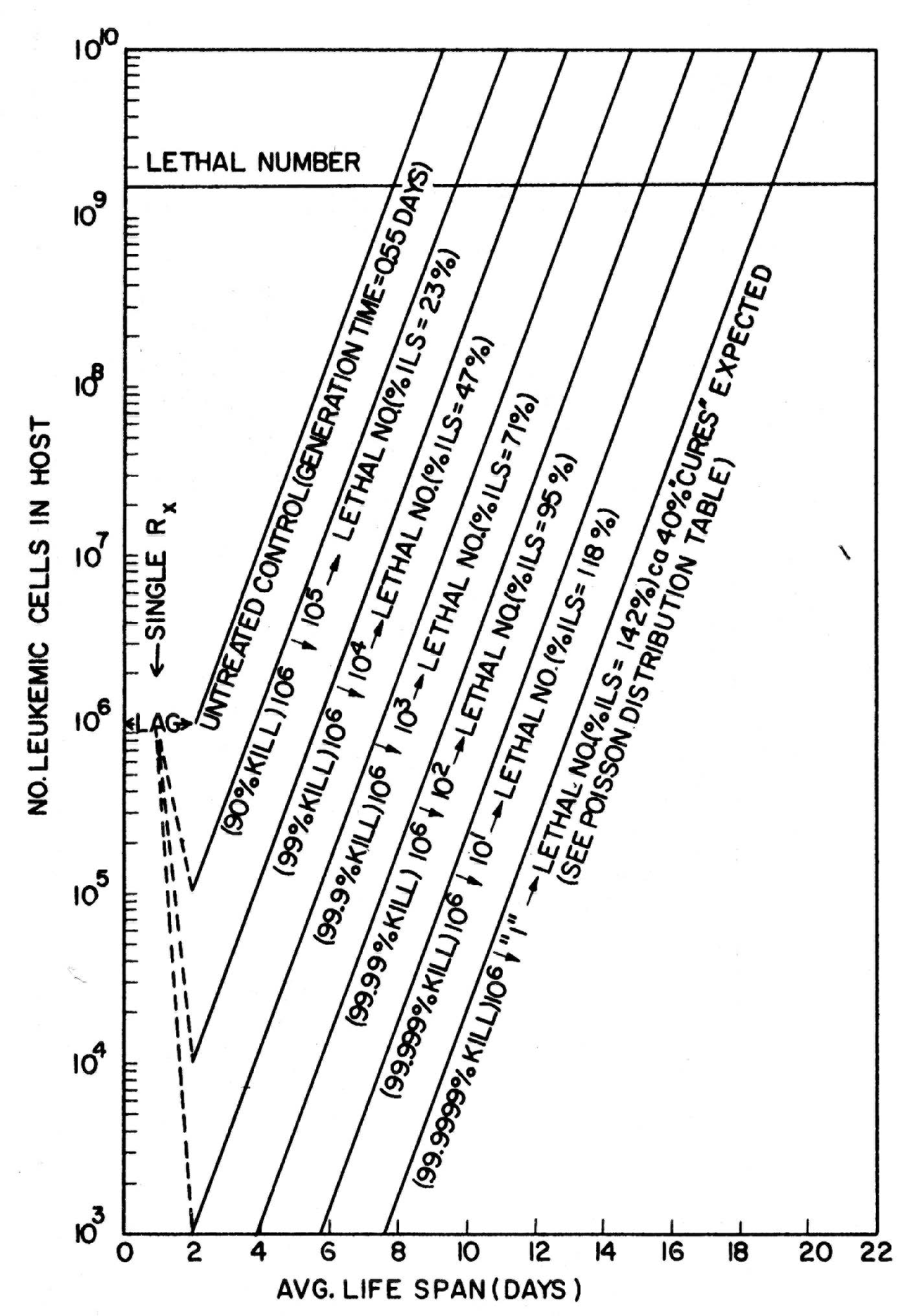


* if kill everything but cancer can differentiate to different stem cells will grow back types of cells, will be resp for metastasis, imp for chemo
* kill mass but CSCs remain, grows back

**THE TOTAL KILL HYPOTHESIS**

* A single cancer cell can multiply and kill the host
* For microbial infections, a “3-log kill” by an antibiotic may be sufficient to allow host defense mechanisms to eradicate the infection
* For successful treatment of cancer, assume that ALL of the cancer cells must be killed

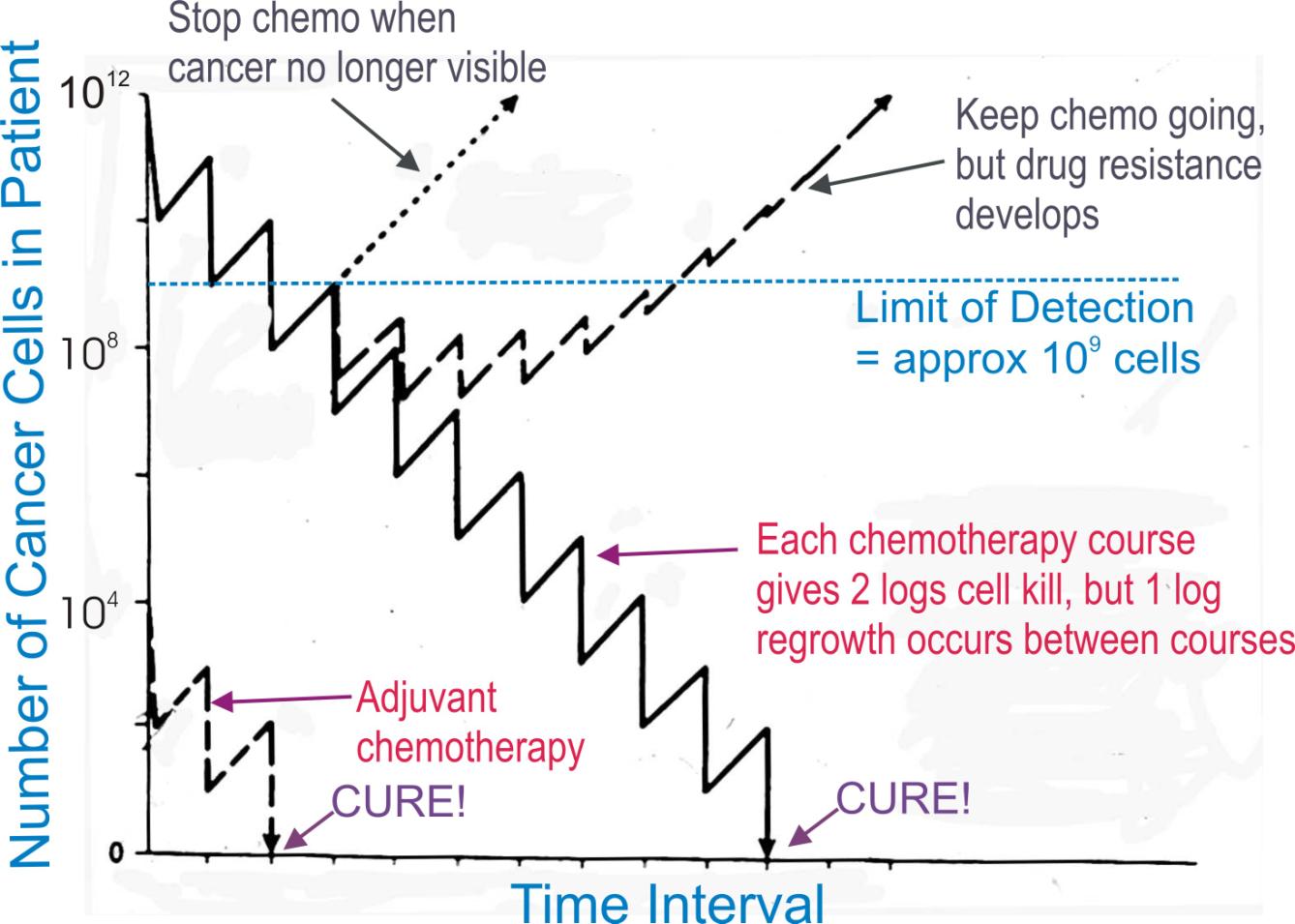
**The Science of Chemotherapy**

* L1210 Mouse Lymphoma: Howard Skipper’s work (1960’s)
  + Rapidly growing tumours
  + Initially used animal survival to infer cancer cell killing in vivo
  + Based on relation between number of cells inoculated and survival
* Treatment with a given dose of an antineoplastic drug will kill a constant fraction of the total cancer cells present
  + 🡨CTL (CD8 T cells) kill tumors
* **Fractional cell kill** of L1210 lymphoma inoculated at 1x106 *in vivo*
* Single treatment with chemotherapy drug
* Effect on lifespan with increasing log cell kill
* *Even though you get a lot of cancer cell, difficult to achieve cure!*
* ’

THE BASIC CLINICAL APPROACH TO CANCER CHEMOTHERAPY

* Because of the Total Kill Hypothesis and the Log Kill Hypothesis, surgery or radiation therapy are used whenever possible for solid tumors. Chemotherapy is used as adjuvant treatment.
* Because nearly all antineoplastic agents are highly toxic to normal cells, intermittent therapy is used.
  + Long term therapy bad and would kill pt prob

**CLINICAL IMPLICATIONS OF FRACTIONAL CELL KILL**

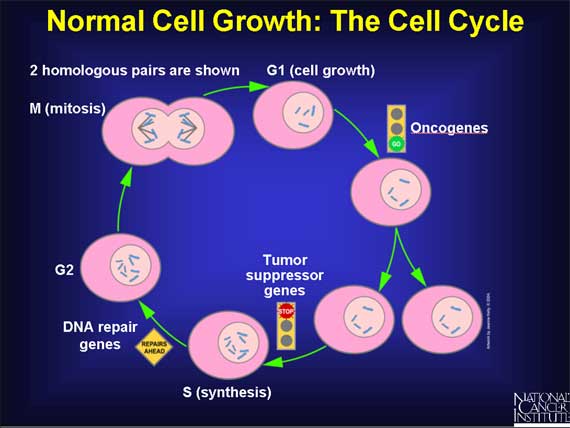


* ↑ reduce 1st by surgery then adjuvant chemotherapy

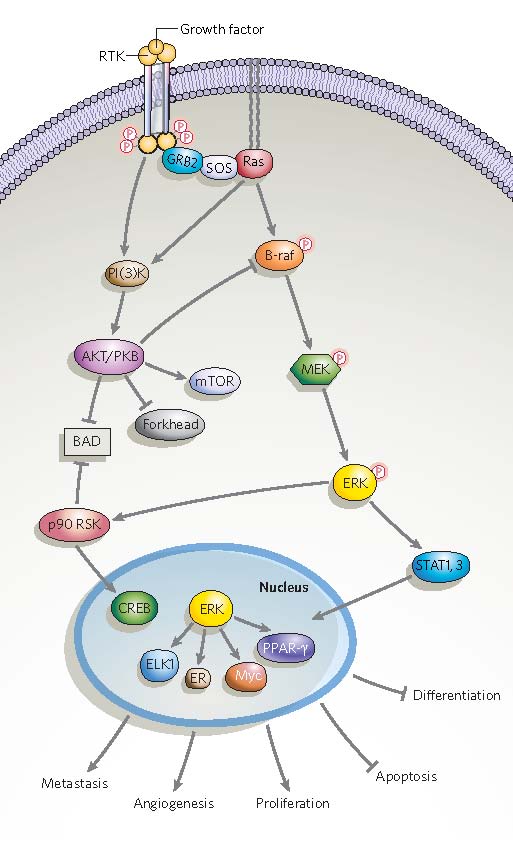
**THE EFFICACY OF ANTINEOPLASTIC DRUGS DEPENDS ON THEIR ABILITY TO KILL CANCER STEM CELLS, WHICH ARE CAPABLE OF DIVIDING**

Description: 2neopt15

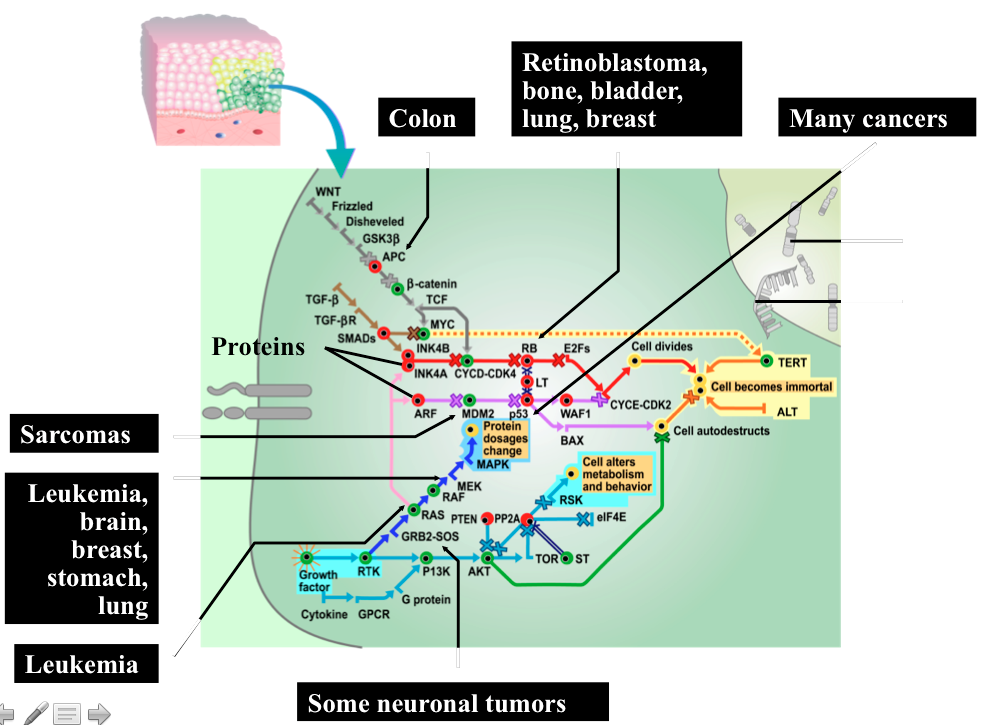
**ETIOLOGY OF CANCER**

* Genetic mutations are largely responsible for the generation of malignant cells.
* Two major categories of mutated genes are oncogenes and tumor suppressor genes
* Oncogenes are abnormal forms of normal genes (proto-oncogenes) that regulate cell growth.
  + Ex: Bcr-abl, Ras (colon cancer)
* Mutation of these genes may result in direct and continuous stimulation of the molecular biologic pathways that control cellular growth and division.
* Tumor suppressor genes are inherent genes that play a role in cell division and DNA repair and are critical for detecting inappropriate growth signals in cells.
  + Ex: p53 and Rb
* If these genes, as a result of inherited or acquired mutations, become unable to function, genetic mutations in other genes can proceed unchecked, leading to neoplastic transformation.
  + 

**RAS-MAPK (MAP KINASE)**

* Many tyrosine kinases participate in **signaling cascades** that trigger cell division, in response to signals like growth factors
  + Are normally tightly regulated by the cell to control proliferation
  + Mutation can change kinases into **oncogenes** (= cancer-causing genes) that are turned on **constitutively** (= constantly), instead of just when cell gets the signal to start dividing
  + link bw obesity/diabetes linked to cancer
    - possible reason is insulin signalling via ras
* 

**CANCER: A COMMUNICATION FAILURE**



**CANCER CHEMOTHERAPEUTIC AGENTS**

* They are classified into:
  + **Cell-cycle non specific agents(CCNS):** are cytotoxic in any phase of the cycle even on G0 phase and so are more effective against large slowly growing tumors.
    - **E.G.Bleomycin.**
  + **Cell-cycle specific (CCS):** are cytotoxic on all phases but not on cells out of the cycle(at G0 ) and so are more effective against rapidly growing tumors. Work better in combination than alone
    - **E.G. Mitomycin, doxorubicin,….etc.**
  + **Phase specific :** act on specific phase of the cycle
    - **E.G.Vinca alkaloids act more in M-phase ,antimetabolites mainly act on S-phase.**

**ANTICANCER DRUGS**

* **There are three Major Groups of Anticancer Drugs:**
  + **1) Cytotoxic Drugs (largest group)**
    - Alkylating agents
    - Antimetabolites
    - Antitumor antibiotics
    - Plant alkaloids
    - Miscellaneous cytotoxic drugs
  + **2) Hormones and hormone antagonists**
    - These are among the best-tolerated chemotherapeutics because they target specific receptors, and thus only specific cell types e.g. Tamoxifen
  + **3) Immunomodulators**
    - -Immunostimulants, including interferons and interleukins
    - -Immunosuppressant

**RESISTANCE TO CHEMOTHERAPY**

* **Resistance to chemotherapy may develop by several mechanisms:**
* Decrease in the amount of drug uptake by cancer cells
  + E.G. Methotrexate
* Increase in the amount of drug efflux by cancer cells. (Transporters=P-glycoprotein).
  + E.G. Vinblastine ,doxorubicin, bleomycin, etapsoid….
* Decrease or alteration in target molecule sensitivity – this is caused by mutation in the molecule targeted by the drug
  + E.G. Methotrexate, Mercaptopurine, doxorubicin
* Increase in DNA repair, ability of the cell via an increased expression of DNA repairing enzymes.
  + E.G. Alkylating agent

**TOXICITY OF ANTINEOPLASTIC DRUGS**

* Many of the common adverse effects of antineoplastic drugs are related to their usual target: dividing cells.
* Many anticancer drugs (esp. alkylating agents) are mutagens and can cause the rise of neoplasms ten or more years after the original cancer was cured.
  + nonspecific, so was affecting normal cells as well
* Teratogenic effects (birth defects)
* Infertility

**GENERAL SIDE EFFECTS OF ANTINEOPLASTIC DRUGS:**

* Normal cells in the body that tend to be injured the most due to chemotherapy are those which have a high growth fraction. Those are bone marrow, GI Tract, hair follicles and reproductive organs.
* Leading to the following:
  + Alopecia - hair loss
  + Myelosuppression-bone marrow loss
  + Low WBC count- low immunity
  + Ulceration of the mouth and GI tract (mucositis)
  + Increased serum uric acid, potassium, phosphate, and calcium
    - ↑ uric acid can cause gout
  + Nausea/vomiting

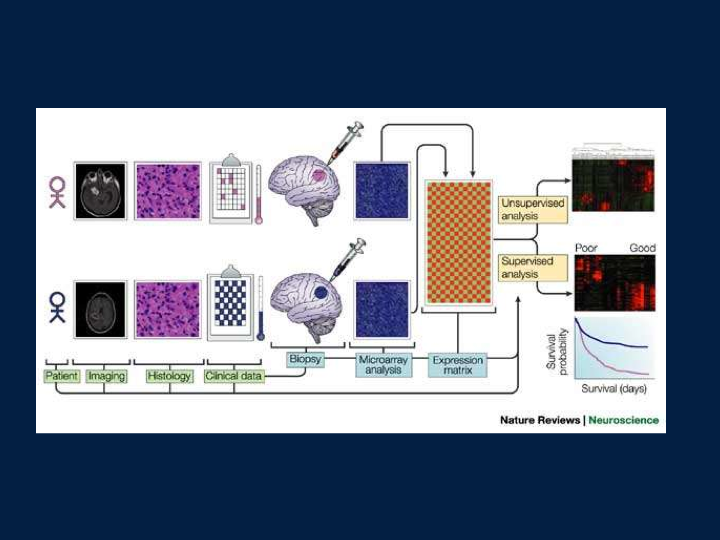
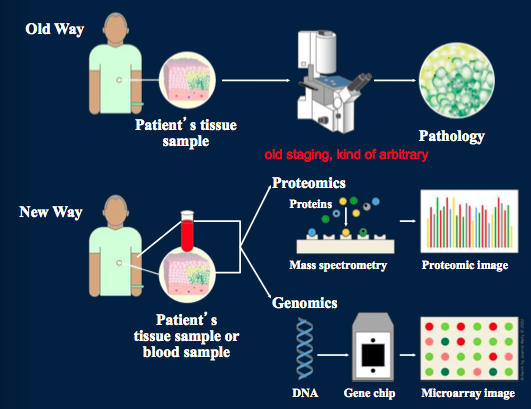
**PALIFERMIN (KEPIVANCE)**

* Used in the prevention or treatment of mouth ulcers arising from high-dose chemotherapy in hematologic malignancies
  + mucisitis from I and I lectures
* It binds to the human keratinocyte growth factor (KGF) receptor on buccal cell surfaces.
* ThebindingactivatestheRas-MapK(Mapkinase)signaling pathway which leads to the transcriptional activation of many proteins important for cell growth and survival.
* KGF increases proliferation of endothelial cells (but not hematopoietic cell lineages, because they lack KGF receptor).

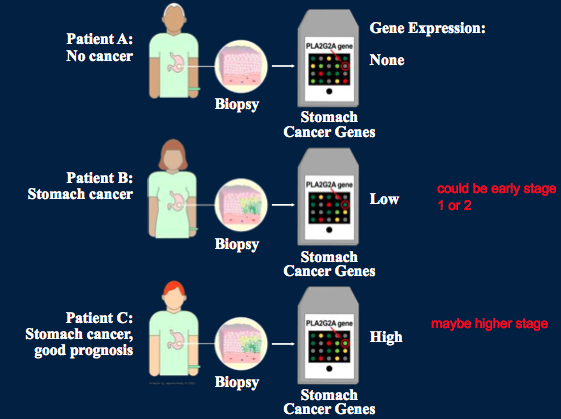
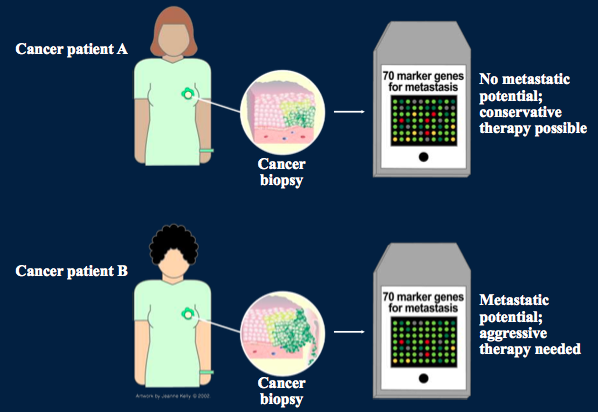
**CONTROL OF NAUSEA ASSOCIATED WITH CANCER CHEMOTHERAPY**

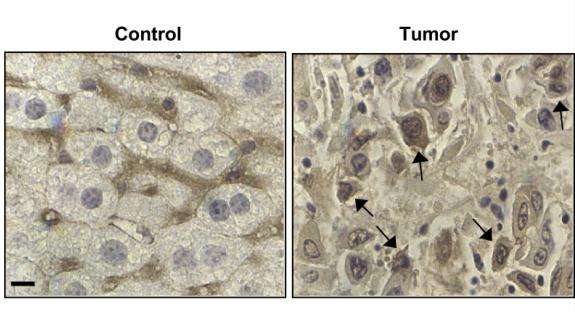
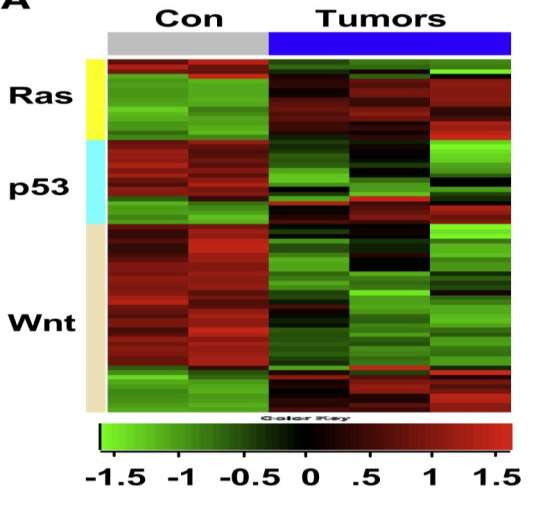
* Serotonin 5HT3 receptor antagonists: Ondansetron and Granisetron
* Corticosteroids: Dexamethasone
* Two kinds of emesis to consider:
  + ACUTE EMESIS, usually controlled with 5HT3 antagonists and steroids.
  + DELAYED EMESIS, Less frequent, but poorly controlled.

**MOLECULAR DIAGNOSTICS**



**CANCER-SPECIFIC GENE EXPRESSION POTENTIAL MARKERS FOR METASTASIS**

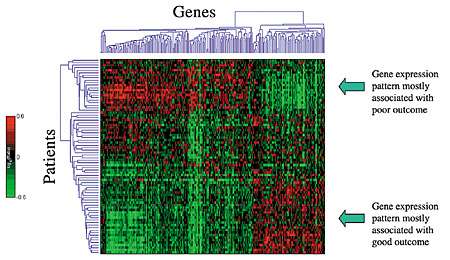
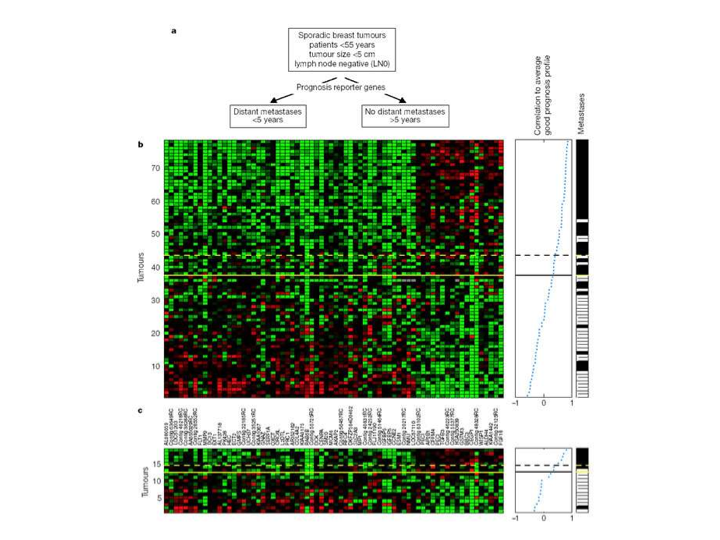
 

* Green less, red more in this microarray. pseudocolor so can be changed.
* can see in control, has less RAS oncogene than tumor. opposite for p53, highly active in control but turned off tumor

**GENE EXPRESSION PROFILING PREDICTS CLINICAL OUTCOME OF BREAST CANCER**

* There will be no q's on predict outcome of pt. just know this tech is out there

maybe help determine tx route

**ANTINEOPLASTIC DRUGS 1**

* Objectives and Preclass Q’s
* what alklylating agent causes hemorrhagic cystits
* major SE of nitrusureas? strange SE of busulfans?
* mech action of cisplatin?
* Describe the mechanism of action of various individual anticancer drugs under each class.
* Explain the bioactivation pathways required for the action of cyclophosphamide.
* Describe the intracellular activation pathways of different antimetabolites.
* Explain the use of antidote in high methotrexate therapy.
* List the major therapeutic indications of various anticancer drugs.

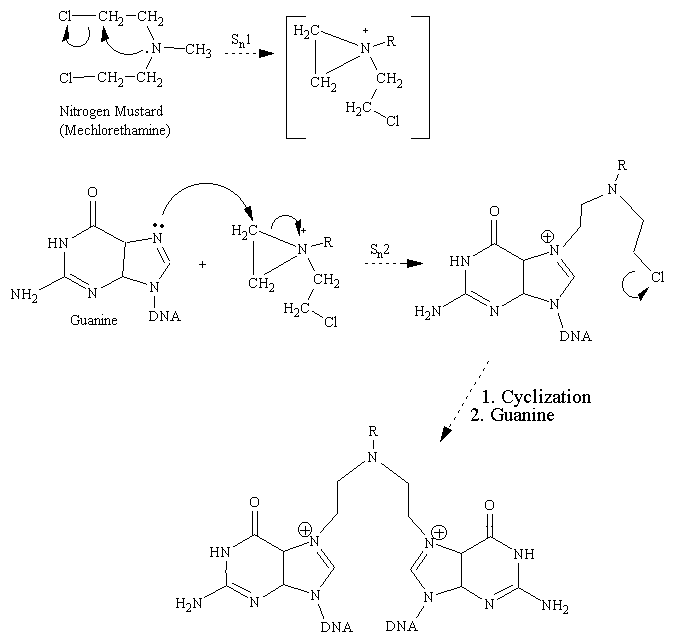
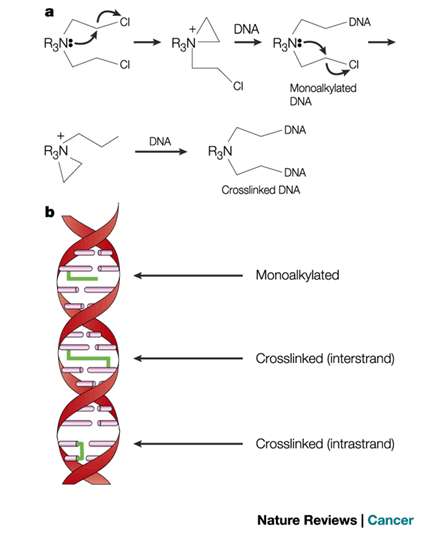
**ALKYLATING AGENTS**

* A brief history...
  + Created by the Germans in World War I  – most effective chemical used in that war.
  + If respirators were not worn, the death rate was about 50 percent.
  + Any part of the body exposed will suffer burns on the skin to severe irritation of lung tissues if the gas is inhaled.
  + Mustard gas used in WWI and WWII
  + Autopsy specimens of soldiers/civilians exposed to mustard gas (or blankets of soldiers exposed to mustard gas) demonstrated profound myelosuppression.
    - Responses in humans found, albeit short-lived (Goodman, *JAMA*, 1946).
  + Nitrogen mustards are nonspecific DNA alkylating agents.
  + Someone thought good idea to put in liquid form and put it in cancer pt. change R grps to see what happened

**CHEMICAL REACTIVITY OF THE NITROGEN MUSTARD GROUP:**

It crosslinks guanine Ethyleneimmonium ion

**Highly reactive**

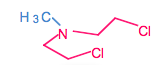


* N7 bind inter- or intra-strand linkage causes this to break

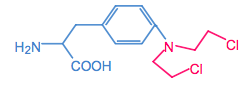
**ALKYLATING AGENTS**

* Attacks N7 of guanine residues of DNA, creating the potential for intrastrand-interstrand DNA crosslinking
* These DNA molecules are ineffective and no longer capable of division
* result in DNA damage and chromosomal breaks
* Also mutagenic
* in mitosis

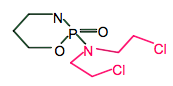
**ALKYLATING AGENTS: The Nitrogen Mustards:**

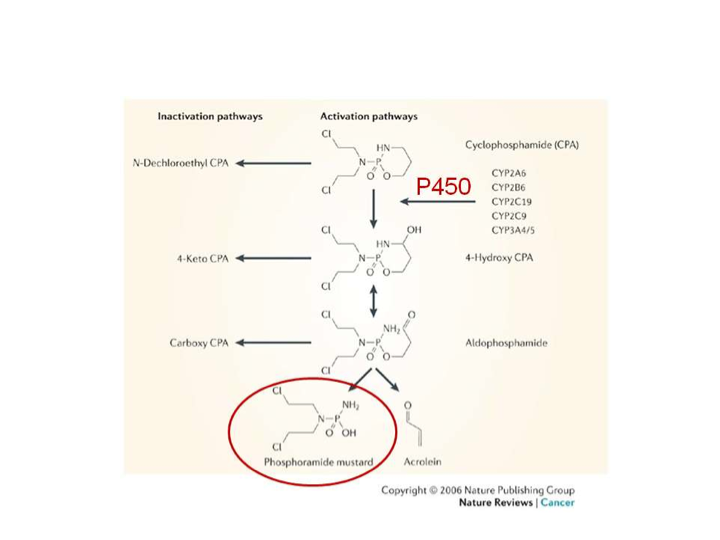
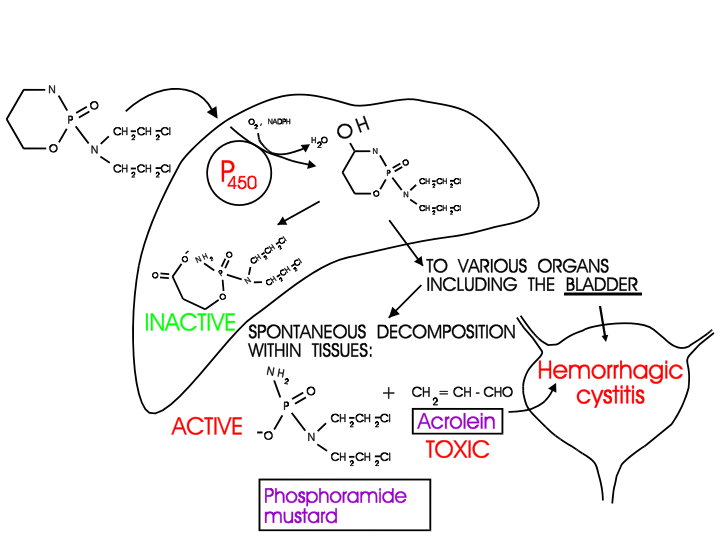
**MECHLORETHAMINE**:

* Mechlorethamine was the first nitrogen mustard found useful for treatment of cancer.
* It is still used as part of the MOPP combination of drugs used to treat Hodgkins lymphoma.
  + MOPP
    - mechlorethemine
    - oncovin
    - procarbazine
    - prednisone
    - (prob won't ask the list, just know mechlorethamine part of it and used to tx hodgkins)
* Short half life in blood (few minutes)
* It is extremely reactive, and will rapidly hydrolyze in water. Thus, it is only very useful for liquid tumors (lymphomas and leukemias).
* It does not have time to penetrate into solid tumors before hydrolyzing to inactive metabolites.
* It must be administered parenterally, and causes blistering necrosis (vesication) of surrounding tissue if leakage occurs from the site of administration.
  + There are some nitrogen musters that can be used for solid tumors we will discuss below

**MELPHALAN**: 

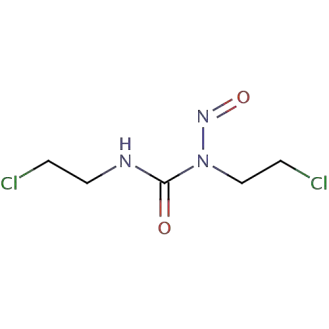
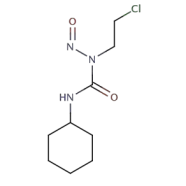
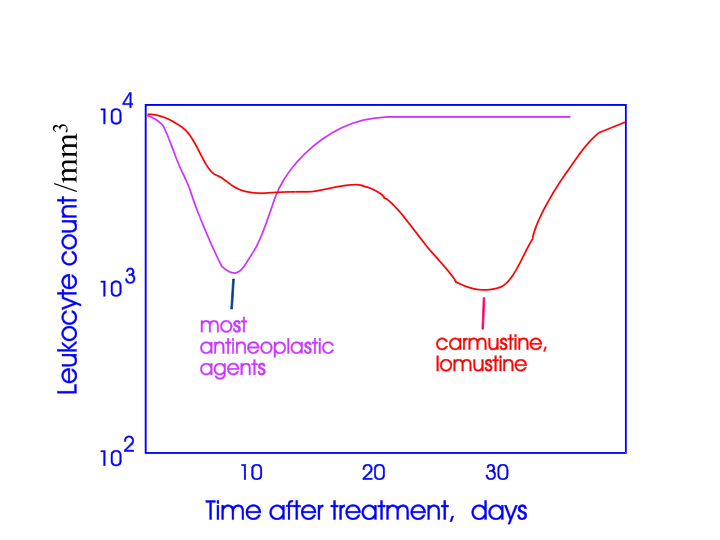
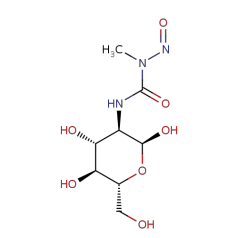
* Melphalan can be given orally or i.v.
  + has a plasma half-life of several hours.
* used to treat multiple myeloma
  + and occasionally ovarian cancer
* Longer half life
* Makes more suitable for solid tumors and palliative in multiple myeloma

**CYCLOPHOSPHAMIDE:**

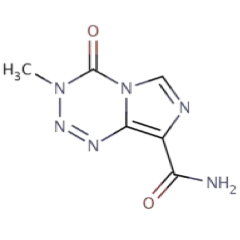
* Most commonly prescribed nitrogen mustard
* Cyclophosphamide is the most frequently used nitrogen mustard
* Can given orally or i.v.,
  + is a prodrug 🡪has to be activated by body
* Cyclophosphamide is used alone or in combination with other medications to treat Hodgkin's lymphoma and non- Hodgkin's lymphoma
* cutaneous T-cell lymphoma (CTCL, a group of cancers of the immune system that first appear as skin rashes)
* low doses for antiinflamm
* multiple myeloma (a type of cancer of the bone marrow)
* and certain types of leukemia
  + – chronic lymphocytic leukemia (CLL),
  + – chronic myelogenous leukemia (CML),
  + – acute myeloid leukemia (AML, ANLL),
  + – and acute lymphoblastic leukemia (ALL).
* Occasionally used to treat retinoblastoma, neuroblastoma, ovarian cancer, and breast cancer.
* **Characteristics**
  + Can be administered orally or i.v.
  + Half life about 6 hours
  + Relatively platelet sparing
  + Less likely than other mustards to produce secondary leukemias
  + A prodrug that requires hepatic oxidation
* Mechanism
  +  side effects from byproduct acrolein
* **Metabolism Of The Nitrogen Mustard Prodrug Cyclophosphamide**
  + 
    - resistance by more CYP 1 potential mech
* **Prevention Of Bladder Toxicity Of Cyclophosphamide**
  + typically just try to keep pt MESNA (MESNEX®) hydrated w/ cyclophosphamide if that doesn't work give mesna
  + Chemically reacts with acrolein in the bladder
  + Oral and i.v. preparations
  + Used to treat cyclophosphamide-induced hemorrhagic cystitis that is not controlled by hydration and diuresis.
  + Treatment of hemorrhagic cystitis that frequently occurs with usual doses of ifosphamide.(another alkylating agent)

**OTHER ALKYLATING AGENTS**

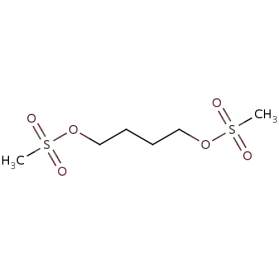
**NITROSOUREAS**: **Carmustine** and **Lomustine**

* + 
    - nitrogen backbone act by crosslinking
  + 
    - double bond O and chlorine
* Act by cross-linking: DNA alkylation
  + like nitrogen mustards
* Highly lipid soluble and can cross the blood–brain barrier
  + making them especially useful for treatment of CNS cancers
    - eg: for cns cancer which alkylating agent would be best? this guy
* Delayed bone marrow suppression
  + may take 6 weeks to recover function following treatment
  + delayed bone marrow suppression is side effect
    - 
* **Streptozocin**:
  + 
    - sugar attached to nitrogen backbone
  + sugar-containing nitrosourea
  + minimal bone marrow suppression
  + effective in insulin-secreting islet cell pancreatic carcinoma and sometimes in non- Hodgkin's lymphoma
  + can induce diabetes in experimental animals
    - actually used to induce diabetes in animals for research probably

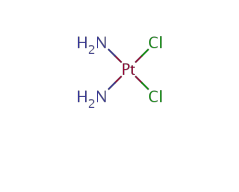
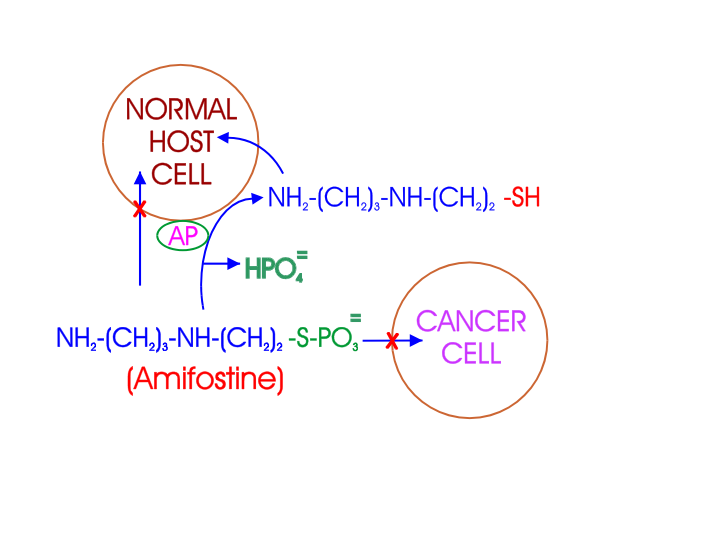
**TEMOZOLOMIDE**

* 
* an oral alkylating agent
* Used for treatment of anaplastic astrocytoma refractory to nitrosoureas.
  + penetrates CNS
  + newly dx glioblastoma tx as well

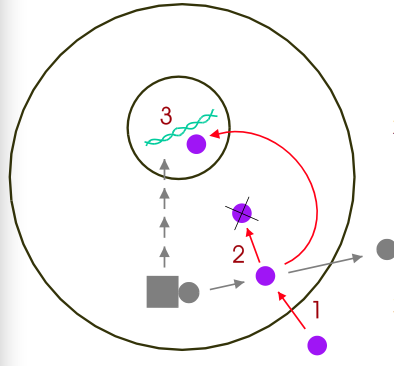
**BUSULFAN**

* 
* An alkylating agent having a selective  immunosuppressive effect on bone marrow
  + can be given orally or i.v.
* Selective for granulocytes
* used for palliative treatment of chronic myeloid  leukemia
* symptomatic relief is provided, but no permanent remission is brought about
* Unusual toxicity: pulmonary fibrosis, or “**busulfan lung**”.
  + life threatening if get this tox

**PLATINUM COORDINATION COMPLEXES**

* **CISPLATIN**
  + 
  + Cross-links N7 of Guanine bases, just like alkylating agents
    - so similarly targets cells rapidly growing
  + Wide spectrum of activity against blood and solid tumors
    - ovary testes head and neck cancers
  + Little effect on bone marrow
  + **Highly emetic**. Requires use of antiemetic drugs
  + **Ototoxicity**: High frequency hearing loss
  + **Renal toxicity**: can be prevented with adequate hydration and diuresis
    - drugs reactive w/ water
    - PROTECTION AGAINST RENAL TOXICITY OF CISPLATIN: **AMIFOSTINE**
    - 
    - norm cell have AP on surf cancer lower expression of this gene. amifostine cannot penetrate cells w/o AP and protect vs cisplatin
    - Susceptible cancer cells express little alkaline phosphatase (AP)
    - Amifostine metabolite reacts with cisplatin
* **CARBOPLATIN**
  + resistant to cisplatin then have resistance to carboplatin as well
  + Less renal and GI toxicity than cisplatin
  + Dose limiting toxicity is bone marrow suppression
  + Useful for most of the same cancers as cisplatin except that head & neck, esophageal, and germ cell cancers may be more susceptible to cisplatin
* **OXALIPLATIN**
  + wasn't clear what he said. maybe upregulate p53 or works thru p53
  + Can treat some cancers that have become resistant to cisplatin or carboplatin

**MECHANISMS FOR DEVELOPMENT OF RESISTANCE TO ALKYLATING AGENTS**



1. Decreased uptake, loss of choline uptake system
2. Increased biotransformation, increased glutathione or metallothionein biosynthesis
3. Altered DNA repair

* Mechanism:
  + Increased capability to repair DNA lesions
  + Decreased transport of the alklating drug into the cell
  + Increased production of gluthathione and glutathione-associated proteins
    - needed to conjugate the alkylating agent
  + Or increased gluthathione S-transferase activity
    - Catalyzes the conjugation